Intervirology

Reprint
Publisher: S. Karger AG, Basel
Printed in Switzerland

'Viruses Seeking Diseases/Diseases Seeking Viruses'

Intervirology 1993;35:208–218

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Bovine Spongiform Encephalopathy: An Appraisal of the Current Epidemic in the United Kingdom

Key Words
Bovine spongiform encephalopathy
Epidemiology
Food-borne infection
Species barriers
Selection of agent strains

Summary
Bovine spongiform encephalopathy (BSE) is a food-borne infection of cattle caused by the use of contaminated meat and bone meal in concentrated feeds. The UK epidemic was initiated by a sudden exposure to infection in 1981–1982, which was associated with a dramatic reduction in the use of organic solvents in the manufacture of meat and bone meal. This change almost certainly removed two partial disinfection steps and allowed enough contamination with a scrapie-like agent to infect cattle. Although it is assumed that the epidemic originated with scrapie infection crossing the species barrier, cattle-to-cattle recycling of infection, via feed, amplified the epidemic very considerably. There would have been a strong tendency for recycling to select a single cattle-adapted strain of agent, and this strain of BSE could well be different from scrapie. There is evidence to support both predictions. Because the median incubation period of BSE is 4–6 years, clinical cases did not appear until 1985–1986, by which time the recycling of infection in cattle was probably well established. However, the average food-borne exposure to infection has remained low resulting in a mainly sporadic occurrence of BSE. Signs of an imminent decline in the epidemic were unmistakable early in 1993, which is over 4 years after the feeding of ruminant-derived protein was banned to prevent new infections of cattle.

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Table 1. The number of histologically confirmed cases of BSE in Great Britain each year from 1988 to 1992, and the percentage increase compared to the previous year

	1988	1989	1990	1991	1992
Number of cases	2,184[a]	7,136	14,181	25,027	36,192[b]
Increase, %		327	199	176	142

[a] Unpublished data by courtesy of John W. Wilesmith.
[b] The figures for 1992 are provisional.

early epidemiological finding was that exposure to infection must have started suddenly, around the winter of 1981–1982, which implies a change in, perhaps, a single limiting factor [4, 16]. The most likely event at this time was a relatively rapid shift away from the use of solvent extraction (to increase the yield of tallow) in the manufacture of meat and bone meal [8].

Solvent extraction was carried out at high temperatures (about 70 °C) for several hours and, afterwards, the last traces of solvent were removed from meat and bone meal by the direct application of superheated steam. From the physicochemical properties of the scrapie agent, both of these steps would have caused some reduction in scrapie infectivity [17]. Therefore, the loss of these two processing steps probably allowed sufficient infection to survive in meat and bone meal to infect cattle [15, 18].

Age-specific incidence data obtained throughout the epidemic show that clinical cases are rare in 2- to 3-year-old cattle and most common in the 4- to 5-, and 5- to 6-year age groups [9]. Since a majority of cases were exposed to infection during calfhood, this pattern reflects a minimum incubation period of about 2 years and a median of 4–6 years, thus setting the time scales of the epidemic. Although BSE was not recognized until November 1986 [1], the first clinical cases were identified, retrospectively, from April 1985 onwards [1, 4], that is, about 3–4 years after the onset of exposure in 1981–1982. In July 1988, the UK government banned the use of ruminant-derived protein in feeds for all ruminants, with the primary objective of preventing new infections of cattle [19].

At present, there is no evidence to suggest that BSE might become a naturally infectious disease of cattle, in the same way that scrapie is of sheep (by maternal and horizontal spread of infection) [20]. No means of infection has been firmly identified other than by the feeding of concentrated rations containing meat and bone meal [13, 14]. Provided that these situations remain substantially unchanged, the 'ruminant protein ban' should be all that is necessary for the eradication of BSE from the UK. But because of the long incubation periods associated with BSE, it was predicted that the total number of cases would not decline until a majority of the animals born before the ban (July 1988) had reached 4–5 years of age, that is, after the end of 1992. During this time, the annual number of BSE cases in Great Britain increased by more than 15-fold (table 1).

In practice, the full effectiveness of the ban was delayed for several months while the feedstuffs manufactured before the ban was

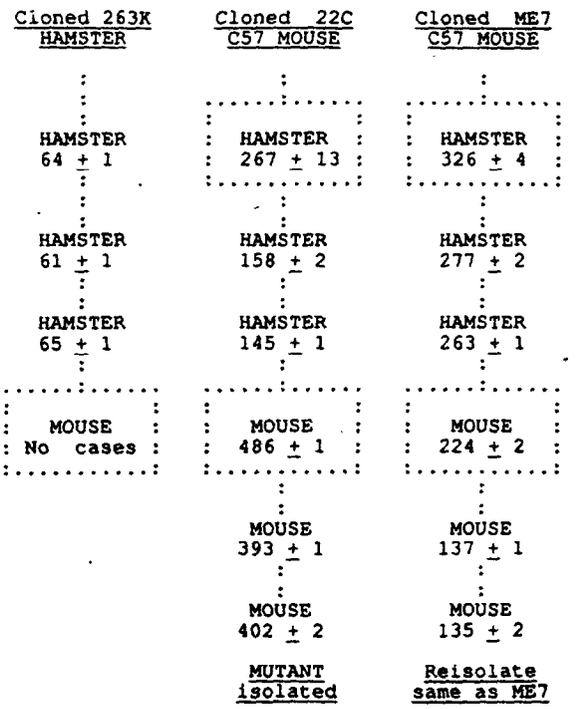

Fig. 1. Variation in the species barrier with different strains of cloned scrapie agent. Scrapie strains were intracerebrally passaged, using homogenates of scrapie-affected brain, from C57BL mice to Syrian hamsters (22C and ME7), and then to C57BL mice (22C and ME7) or to CW mice (263K). Both mouse strains are *Sinc* s7s7. The data are taken from figures 3 and 4 of Kimberlin et al. [25]. Incubation periods are shown in days as mean ± SEM. In the 22C passage line, the strain reisolated in mice was a mutant with quite different incubation period and neuropathological properties from those of 22C. In the ME7 passage line, the strain reisolated in mice was identical to ME7. The 263K strain of agent did not produce clinical disease in mice after observation periods of up to 730 days.

passaged through hamsters and reisolated in mice, the reisolate was the same as the original ME7. In this case, the species barrier effects were due entirely to the adaptation of the hamster-passaged ME7 agent to mice during the first passage (fig. 1) [25]. There is good evidence that the donor species effect is largely dependent on the *PrP* gene. An elegant illustration of this is that the seemingly absolute species barrier to the 263K strain of hamster scrapie in mice did not exist in transgenic mice that expressed the hamster *PrP* gene; in terms of incubation period, the transgenic mice developed scrapie just as though they were hamsters [26].

'Strain selection' is the other phenomenon associated with crossing the species barrier, and it may involve preexisting strains of agent or mutant strains. Mutations occur commonly as 'mistakes' during the multiplication of most microbial agents and the scrapie group of infections is no exception [24, 25, 27]. Most mutations have no biological consequences, either because they are not viable or because they do not confer any selective advantage to the mutant strain in the host. But a mutant may have an advantage over the parental strain in a different host. This occurred at some stage during the serial passage of the 22C strain of mouse scrapie in hamsters and

Table 2. Primary transmissions to mice of 4 geographically separate cases of BSE and 1 contemporary case of scrapie

	Strain and (*Sinc* genotype) of mice[a]			
	RIII (*s7s7*)	C57BL (*s7s7*)	VM (*p7p7*)	IM (*p7p7*)
BSE case No. 1	328±3[b]	438±7	471±8	537±7
BSE case No. 2	327±4	407±4	499±8	548±9
BSE case No. 3	316±3	436±6	518±7	561±9
BSE case No. 4	314±3	423±5	514±11	565±8
Greyface scrapie	381±11	404±5	769±16	809±25

[a] The data are taken from table 1 in Fraser et al. [23].
[b] Incubation period in days, mean ± SEM.

One major consequence of recycling is that it would tend to accelerate the selection of a bovine-adapted strain of agent by giving it an advantage over the preexisting strain(s) of sheep scrapie. This is because there would be no donor species effect for the bovine-adapted agent and the development of the epidemic would soon become independent of continuing infections from sheep.

A second consequence of recycling stems from the evidence to be discussed later, that there seems to be little biologically significant variation in any cattle genes that control the incubation of BSE. This means that all cattle would tend to exert a similar selective pressure to yield one major strain or a few strains with very similar properties in cattle. A crude analogy to this selection process can be drawn from figure 1. If a mixture of all three scrapie strains in hamsters was injected into the same mice, a single strain (ME7) would be selected by virtue of its shorter incubation period at first and subsequent passages in mice. Since some strains of scrapie agent vary in their stability to heat, it is conceivable that the rendering process may also have exerted a selective pressure, favoring the most heat-resistant strains.

Recycling would exert a relatively uniform selective pressure on both a preexisting common strain of agent in sheep, and on any mutant strain that arose from it in cattle. Supporting evidence comes from the remarkably similar patterns of incubation period produced by 4 geographically separate isolates of BSE at first passage in a panel of different strains of mice (table 2). Similar results were also obtained with isolates from naturally occurring cases of spongiform encephalopathy in nyala, kudu and domestic cats [23]. The occurrence of disease in these other species is associated with BSE in cattle [18, 30], and the similar behavior of all these primary isolates strongly implicates a single strain of agent whose isolation in mice was not unduly influenced by different donor species effects.

This uniformity is in striking contrast to the many different strains of agent that have been derived from sheep scrapie in the last 25 years [23, 31]. Some of this diversity is undoubtedly the result of the selection of mutant strains after many passages in different species and/or genotypes of laboratory animals [20]. But, equally, some diversity probably reflects a natural variation in the scrapie strains occurring in sheep, as would be expected from a combination of different 'natu-

Table 3. Different responses of sheep and cattle to parenteral injection with scrapie and BSE, respectively (mean ± SEM of the number of animals)

	Incubation period, days	
	short	long
Scrapie injected into sheep[a]		
Swaledale flock No. 1	287 ± 7 (n = 156)	1,207 ± 38 (n = 40)
Swaledale flock No. 2	371 ± 24 (n = 10)	1,382 ± 94 (n = 6)
Swaledale flock No. 3	289 ± 33 (n = 6)	1,271 ± 54 (n = 5)
Swaledale flock No. 4	269 ± 19 (n = 8)	1,186 ± 67 (n = 9)
BSE injected into cattle[b]		
Holstein/Friesian	577 ± 14 (n = 8)	
Jersey	572 ± 14 (n = 8)	

[a] Swaledale sheep were injected subcutaneously with one of two similar pools of infected brains from natural cases of scrapie in Swaledales. The data are taken from table 6 and the text by Davies and Kimberlin [34]. The flocks are identified as follows: flock No. 1 = foundation flock; flock No. 2 = 1975 'control' flock; flock No. 3 = 1976 'control' flock; flock No. 4 = 4th flock. The presence of a single gene (*Sip:* with two alleles) which controls the incubation period of experimental scrapie is indicated by the 3 different responses of the injected sheep: those with a short incubation period, those with a much longer incubation period, and those which did not develop the clinical disease after observation periods of up to 2,557 days.

[b] Cattle were injected intracerebrally and intravenously with pooled material from 4 brains from natural cases of BSE in Holstein/Friesian. The data are taken from Dawson et al. [35] and Dawson and Wells [unpublished]. All the injected cattle developed disease after very similar incubation periods suggesting that there is no allelic variation at a genetic locus in cattle equivalent to the *Sip* gene in sheep.

major role for genetic factors in the occurrence of BSE [4, 33]. Transmission studies revealed a 100% incidence and highly uniform incubation periods in a group of 8 Jersey and 8 Holstein/Friesian cattle that had been injected with BSE (table 3) [7, 35]. This finding is in striking contrast to the results obtained after injecting sheep with scrapie when the response varied according to their *Sip* genotype. Because the *Sip* gene has two alleles, there are three possible genotypes, only two of which developed the clinical disease, but after very different incubation periods (table 3).

The other possible explanation for the sporadic occurrence of BSE cases is that, although the distribution of the infectious agent in meat and bone meal would not have been homogeneous, the *average* exposure of cattle throughout the epidemic was relatively low [15, 18]. This is most clearly revealed by the very small within-herd incidence of BSE from 1988 to 1992 (table 4). The dramatic development in the scale of the epidemic over this time was largely due to an increase in the number of new herds with BSE. Hence the major effect of recycling was to increase the number of batches of meat and bone

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